## REMARKS

Claim Rejections – 35 U.S.C. § 102

Claims 1, 3-9, 11-17, 33 and 34 are rejected under 35 U.S.C. §§ 102(a) and/or (e) as allegedly anticipated by Cotton et al (U.S. Pat. No. 6,369,085; "Cotton") for the reasons set forth in the previous Office Action. According to the Examiner, Cotton specifically discloses the instant compound. Particular attention is directed to Example 1 and column 2, lines 47-50, which states that "[t]he compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of S-omeprazole disclosed in the prior art." Applicants respectfully traverse this basis for rejection.

It has long been the law that anticipation can properly be held only where a prior art document teaches each and every limitation of the rejected claim. *See Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Contrary to the Examiner's position, Cotton does not disclose the instant compound with all its limitations. Claims 1, 3-9, 11-17, 33 and 34 are directed to a crystalline form II of esomeprazole magnesium trihydrate having substantially the same X-ray powder diffraction ("XRPD") pattern as shown in Fig. 1 of the instant specification, a pattern which is not expressly or inherently disclosed by Cotton.

As noted by the Applicants in their Amendment and Response submitted on February 21, 2007 ("2/21/07 Amendment and Response"), even a cursory inspection reveals that the XRPD pattern for the instant crystalline form II of esomeprazole magnesium trihydrate shows, *inter alia*, very prominent peaks at about 4.8 and 18.5 degrees two-theta that are completely absent from the pattern for the esomeprazole

magnesium trihydrate disclosed in Cotton, while the XRPD pattern for the esomeprazole magnesium trihydrate of Cotton shows, *inter alia*, a very prominent peak at about 22.5 degrees two-theta that is completely absent from the pattern for the instant crystalline form II of esomeprazole magnesium trihydrate. (*Compare* Fig. 1 and the table at page 6 of the instant specification with Fig. 1 of Cotton.)

According to the Examiner, the differences in XRPD patterns are not persuasive because XRPD pattern alone does not demarcate the identity of two products. The examiner cites to Davidovich et al., *Am. Phar. Rev.* 7:16 (2004) ("Davidovich") for the proposition that small changes in XRPD patterns can arise as experimental artifacts rather than polymorphism. As evidence of this phenomenon, the Examiner cites to Figures 4.21 and 8.5 of Bernstein, "Polymorphism in Molecular Crystals," pp. 118, 272 (2002) ("Bernstein") as showing that the same compound can have two different XRPD patterns. Applicants submit that, rather than supporting the Examiner's position, Davidovich and Bernstein actually support the conclusion that the instant crystalline form II of esomeprazole magnesium trihydrate and the esomeprazole magnesium trihydrate disclosed in Cotton are distinct polymorphic forms.

First, although Davidovich does state that changes in XRPD patterns can arise from experimental artifacts, such changes are said to be "small." (Abstract, p. 10.) An examination of Figures 2, 3, 5, 6 and 8-10 demonstrates just how small these changes are. In contrast, a comparison of the XRPD data previously described regarding the instant crystalline form II of esomeprazole magnesium trihydrate and the esomeprazole magnesium trihydrate disclosed in Cotton demonstrates quite large changes in XRPD patterns, even allowing for standard error in measurement. Applicants submit that the

large differences between the XRPD patterns for the esomeprazole magnesium trihydrate disclosed in Cotton and the instant crystalline form II of esomeprazole magnesium trihydrate are simply not the type of minor variation contemplated by Davidovich as being due to artifacts rather than true polymorphism. Indeed, Davidovich itself states that "Powder X-ray Diffraction (PXRD) is a powerful tool in identifying different crystalline phases by their unique diffraction patterns." (p. 10.)

Second, although Figure 4.21 of Bernstein does show different X-ray diffraction patterns for sulphathiazole, this example is admittedly "dramatic." (p. 117.) More importantly, Fig. 4.21 does not compare two different powder diffraction patterns, but rather a powder diffraction pattern with an expected pattern calculated from the crystal structure. This explains the conclusion of Bernstein that "almost all of the expected diffraction peaks have been severely suppressed." (*Id.*). The Examiner has provided no evidence or reasoning why such peak suppression would be expected when comparing actual powder diffraction patterns between different esomeprazole magnesium trihydrate preparations.

Regarding Figure 8.5 of Bernstein, the Examiner describes the figure by saying that "[a]lthough there are new peaks, the authors concluded that "it may not be a pure medication", i.e., not a true polymorph." However, Figure 8.5 of Bernstein actually states that "[t]he lower pattern [for Pigment Yellow 17] shows evidence of virtually every peak that appears in the upper pattern [for Pigment Yellow 17], indicating that it may not be a pure modification. Nevertheless, there are diffraction maxima that do appear to be unique to a second form." (p. 273) (emphasis added.) Thus, the authors actually conclude that the Pigment Yellow 17 in Figure 8.5 existed as an unpure mixture of two

different polymorphs, not, as the Examiner asserts, a single form having two different XRPD patterns. This is confirmed by the authors' statement on p. 273 that Pigment Yellow 17 is a "dimorphic system, for which both powder patterns are shown in Fig. 8.5."

Thus, contrary to the Examiner's position, both Davidovich and Bernstein support the use of XRPD analysis to establish polymorphic identity. As noted by Brittain, ed. (Polymorphism in Pharmaceutical Sciences, 1999, p. 235; "Brittain") (of record):

> [D]uring the most common evaluation of drug substances, it is usually sufficient to establish only the polymorphic identity of the solid and to verify that the isolated compound is indeed of the desired structure. For these reasons, the technique of X-ray powder diffraction (XRPD) is the predominant tool for the study of polycrystalline material and is eminently suited for the routine characterization of polymorphs and solvates.

Thus, Applicants submit that, consistent with the references of record, the major differences in their XRPD patterns indicate that the instant crystalline form II of esomeprazole magnesium trihydrate and the esomeprazole magnesium trihydrate disclosed in Cotton are indeed distinct polymorphic forms. As such, the Examiner has failed to make out a *prima facie* case for anticipation of the claimed form. *See Ex parte Havens*, Appeal No. 2001-0091 for U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2001) ("The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed [in the prior art reference] is in the [claimed] crystal form. Therefore, the examiner has not made out a *prima facie* case of anticipation by inherency.").

Accordingly, Applicants maintain that claims 1, 3-9, 11-17, 33 and 34 are not anticipated by Cotton, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 3-9, 11-17, 33 and 34 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cotton in view of Bohlin et al. (U.S. Pat. No. 6,162,816; "Bohlin"), Lindberg et al. (U.S. Pat. No. 6,875,872; "Lindberg"), Haleblian et al. (*J. Pharm. Sciences*, (1969), 58 pp. 911-929; "Haleblian"), Muzaffar et al. (*J. of Pharmacy* (Lahore) 1979, 1(1), 59-66; "Muzaffer"), Chemical & Engineering News, Feb. 2003 ("C&E News"), U.S. Pharmacopia, 1995, pp. 1843-1844 ("USP") and Concise Encyclopedia Chemistry, pages 872-873 (1993) ("CEC") for the reasons essentially set forth in the previous Office Action. According to the Examiner, Cotton teaches the crystalline form of the magnesium salt of esomperazole. Bohlin and Lindberg are said to teach that esomeprazole and its salts can exist in different crystalline states. Muzaffar and Haleblian are said to teach that compounds can exist in amorphous forms as well as crystalline states. C&E News, USP and CEC are said to teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Thus, according to the Examiner, it would appear to one skilled in the art in view of the references that the instant compound would exist in different crystalline forms. Again, no unexpected or unobvious properties were noted by the Examiner. Applicants respectfully traverse this basis for rejection.

The standards for making an obviousness rejection are summarized in MPEP § 706.02(j) as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The instant claims are directed to crystalline form II of esomeprazole magnesium trihydrate having substantially the same XRPD pattern as shown in Fig. 1. The references cited by the Examiner do not disclose, either alone or in combination, this particular polymorphic form.

As explained in Applicants' 2/21/07 Amendment and Response, Cotton discloses a crystalline form of esomeprazole magnesium trihydrate, but does not teach or suggest crystalline form II of esomeprazole magnesium trihydrate having substantially the same XRPD pattern as shown in Fig. 1 of the instant specification. Similarly, while Bohlin discloses that esomeprazole base can exist in amorphous, partly crystalline or substantially crystalline solid states, and Lindberg discloses crystalline esomeprazole magnesium, neither teach nor suggest crystalline form II of esomeprazole magnesium trihydrate having substantially the same XRPD pattern as shown in Fig. 1 of the instant specification. The ancillary references cited by the Examiner merely provide general background information relating to the study and preparation of polymorphs or case histories of specific polymorphic compounds (none of which is esomeprazole magnesium trihydrate), and thus add nothing over the primary references.

As such, none of the cited references, alone or in combination teach or suggest the instantly claimed compound with all its limitations. This alone is enough to overcome the Examiner's obviousness rejection. *See Ex parte Havens*, Appeal No. 2001-0091 for U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2003) ("The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection . . . . The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.") (emphasis added).

As noted in Applicants' February 21, 2007 Response, the proper test for obviousness in this case is not whether the existence of esomeprazole magnesium trihydrate polymorphs is suggested by the prior art, but whether it would have been obvious to make the particular esomeprazole magnesium trihydrate claimed in the instant application based on the prior art:

> The law of § 103 requires quite a different inquiry from that conducted by the ALJ. Thee correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

*Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 892 F.2d 1050, 1989 WL 147230 (Fed. Cir. Dec. 8, 1989) (unpublished decision) (emphasis added).

Here, the references cited by the Examiner suggest at most the possibility of other esomeprazole magnesium trihydrate polymorphs. The Examiner has pointed to nothing in the cited references, however, that would suggest to one skilled in the art the particular

form claimed in the instant application, or a method for its preparation. *See Ex parte Polniaszek*, Appeal No. 2001-1805, U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2003) ("The prior art relied upon by the examiner does not teach this specific polymorph as claimed by the appellants. The Examiner failed to demonstrate that the prior art even recognized that the claimed compound exists in different polymorphic forms, or that there is a known or obvious way to manufacture the specific polymorphic form claimed."). In fact, as noted in Applicants' February 21, 2007 Amendment and Response, CEC (p. 32) states that "no method yet exists to predict the polymorphs of a solid compound with significant certainty."

Because of this uncertainty, Applicants maintain that no *prima facie* case of obviousness of claims 1, 3-9, 11-17, 33 and 34 has been made out by the Examiner. *See Ex parte Andrews*, Appeal No. 2002-0941 for U.S. Pat. Appl. No. 09/166,445, now U.S. Pat. No. 6,713,481 (BPAI 2003) ("[T]he examiner has not adequately explained how a person having ordinary skill would have been led from 'here to there,' i.e., from the [prior art] compound having formula I to the crystalline polymorph form I recited in claims 1 through 5."); *Ex parte Portmann*, Appeal No. 2003-1199 for U.S. Pat. Appl. No. 09/125,329, now U.S. Pat. No. 6,740,669 (BPAI 2004) (same).

Citing *In re Cofer and Ex parte Hartop*, the Examiner still appears to be taking the position that new solid state forms are *per se* unpatentable over the originally identified compound or previously identified solid state forms of the same compound. As noted in Applicants' 2/21/07 Amendment and Response, however, such a rule is inconsistent with the law on obviousness. *See Ex parte Andrews*, *supra* (quoting *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995) ("The use of *per se* rules flouts § 103 and the

fundamental case law applying it. . . . [R]eliance on *per se* rules of obviousness is legally incorrect and must cease.").

Here, as discussed above, the references cited by the Examiner neither disclose nor suggest the crystalline form II of esomeprazole magnesium trihydrate disclosed and claimed in the instant application, nor a method for its preparation. As such, unexpected properties need not be demonstrated because a *prima facie* case of obviousness has not been made under the proper test described above.

Accordingly, Applicants maintain that claims 1, 3-9, 11-17, 33 and 34 are not unpatentable over Cotton in view of Bohlin, Lindberg, Haleblian, Muzaffar, C&E News, USP and CEC, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 112

Claims 33 and 34 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement for the reasons essentially set forth in the previous Office Action. According to the Examiner, there is a lack of description as to whether the compositions are able to maintain the compound in the crystalline form claimed. In particular, the Examiner states that processing a compound into a pharmaceutical composition could create a different form. Applicants respectfully traverse this basis for rejection.

Claims 33 and 34 are directed to a solid pharmaceutical composition comprising crystalline form II of esomeprazole magnesium trihydrate having substantially the same XRPD pattern as shown in Fig. 1 of the instant specification, and a method for reducing gastric acid secretion in a subject comprising administration of such a solid pharmaceutical composition. As noted in Applicants' February 21, 2007 Amendment

and Response, the claims contain no limitation requiring that the crystalline form be maintained indefinitely, or that it be the only form present, and Applicants submit that it is error to read such a limitation into the claims. Any esomeprazole magnesium trihydrate not having substantially the same X-ray diffraction pattern as shown in Figure 1 is outside the scope of the claims. Applicants maintain that the instant specification clearly describes and enables the preparation of compositions comprising crystalline form II esomeprazole magnesium trihydrate having substantially the same X-ray diffraction pattern as shown in Fig. 1 of the instant specification, and methods of treatment comprising the same. *See, e.g.*, page 11, line 26 to page 15, line 12. Furthermore, the specification clearly describes and enables methods for identifying and monitoring the presence of crystalline form II esomeprazole magnesium trihydrate in the claimed composition before, during and after its preparation. *See, e.g.*, page 5, line 32 to page 9, line 22.

With regard to the Examiner's contention that polymorphs may undergo transformation when formulated into compositions, Applicants note that several of the references cited by the Examiner explain that such transformation can be very slow (on the order of years) owing to the relative stability of the metastable form. As Muzaffar notes at page 60:

> When the rate of conversion of a metastable form is so slow as to be negligible, the solubility of the compound will be maximal and will have a faster rate of dissolution and hence absorption. This biopharmaceutical property of the polymorphs could be explained for achieving better results in the formulation of drugs, especially in the unit disage forms of the drugs.

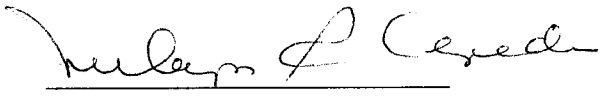
Thus, even assuming that crystalline form II esomeprazole magnesium trihydrate is a metastable form (mere conjecture at this point), its possible transformation at some point in the future does not detract from its utility while in the claimed form. Again, any esomeprazole magnesium trihydrate not having substantially the same X-ray diffraction pattern as shown in Figure 1 is outside the scope of the claims.

Accordingly, Appellants maintain that claims 33 and 34 are not invalid for lack of adequate written description, and reconsideration of this basis for rejection is respectfully requested.

## CONCLUSION

Applicants submit that claims 1, 3-9 and 11-17, 33 and 34 are now in condition for allowance, early notice of which would be appreciated. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number indicated below to discuss the same. No fees are believed due at this time. If, however, any fees are due, the Commissioner is authorized to charge any such fee to our Deposit Account No. 50-3221.

Respectfully submitted,



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